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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,912	10/04/2004	Takahiro Ito	0020-5301PUS1	4489

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
LAU, JONATHAN S	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
05/06/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/509,912	ITO ET AL.	
	Examiner	Art Unit	
	Jonathan S. Lau	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 Apr 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-23 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20* is/are allowed.

6)☒ Claim(s) *21-23 and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Withdrawal of Finality

The Finality of the Office Action mailed 3 Dec 2009 is **withdrawn**.

This Office Action is responsive to Applicant's Remarks, filed 16 Apr 2010.

The instant application is the 371 national stage entry of PCT/JP03/04745, filed 15 Apr 2003; and claims benefit of foreign priority document JP 2002- 112864, filed 16 Apr 2002; an English language translation of this foreign priority document has been made of record and the claim of foreign priority is perfected.

Claims 20-23 and 25-30 are pending and examined on the merits herein.

Rejections Withdrawn

Applicant's Remarks, filed 16 Apr 2010, with respect to claim 20 rejected under 35 U.S.C. 102(b) as being anticipated by Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) has been fully considered and is persuasive, as Applicant remarks are persuasive that Okuno et al. describes % w/w of T-2513 (drug) moieties present within compound T-0128 and not a concentration of compound T-0128 in solution. Okuno et al. describes the synthesis of T-0128 by reference to US Patent 5,837,673 (page 2989, left column, paragraph 2). US Patent 5,837,673 (cited in PTO-892) describes the compound in terms of % by weight describing the ratio of

polysaccharide to camptothechin compound (column 6, lines 25-35), consistent with Applicant's remarks. Therefore Applicant's remarks are persuasive that Okuno et al. does not disclose all limitations of the instantly claimed invention.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 16 Apr 2010, with respect to claim 22 rejected under 35 U.S.C. 103(a) as being unpatentable over Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) has been fully considered and is persuasive, as Applicant remarks are persuasive that Okuno et al. does not teach all limitations of the instantly claimed invention as discussed above.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 16 Apr 2010, with respect to claim 20, 22 and 25-28 rejected under 35 U.S.C. 103(a) as being unpatentable over Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) in view of Harada et al. (Journal of Controlled Release, 2000, 69, p399-412, of record) has been fully considered and is persuasive, as Applicant remarks are persuasive that Okuno et al. does not teach all limitations of the instantly claimed invention as discussed above and is not remedied by Harada et al.

This rejection has been **withdrawn**.

Applicant's Remarks, filed 16 Apr 2010, with respect to claim 20-23 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) in view of Harada et al. (Journal of Controlled Release, 2000, 69, p399-412, of record) and further in view of Inoue et al. (WIPO Publication WO97/46260, published 11 Dec 1997, of record) and in view of the '817 Patent (US Patent 5,340,817, issued 23 Aug 1994, of record) has been fully considered and is persuasive, as Applicant remarks are persuasive that Okuno et al. does not teach all limitations of the instantly claimed invention as discussed above and is not remedied by Harada et al., Inoue et al. and the '817 Patent.

This rejection has been **withdrawn**.

Claim Objections

Claims 20-23 are objected to because of the following informalities: upon further review, claims 20-23 each recite the typographical error "pulluran" in place of "pullulan". Appropriate correction is required.

The following are new grounds of rejection.

Claim Rejections - 35 USC § 103

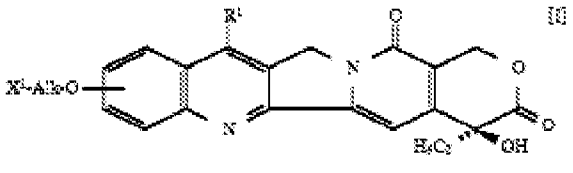
The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

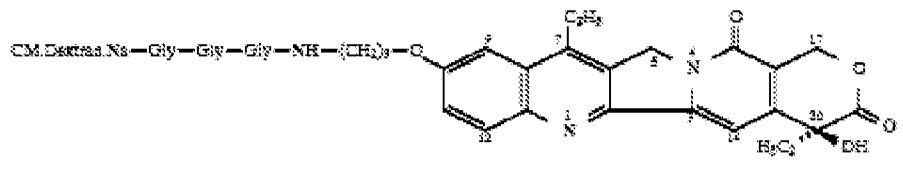
This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 20 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsujihara et al. (US Patent 5,837,673, issued 17 Nov 1998, cited in PTO-892) in view of Harada 2001 (Journal of Controlled Release, 2001, 71, p71-86, cited in PTO-892) and Fassberg et al. (Journal of Pharmaceutical Sciences, 1992, 81(7), p676-684, cited in PTO-892) and Bates et al. (Analytical Chemistry, 1978, 50(9), p1295-1300, cited in PTO-892).

Tsujihara et al. teaches a camptothecin derivative of formula



bound to a polysaccharide having carboxyl groups via a peptide (abstract) such as the embodiment



(spanning top of columns 49 and 50), also named compound T-0128. Tsujihara et al. teaches the compound in the form of a liquid preparation such as for intravascular injection (column 10, lines 20-25) and optimizing the dosage of said compound (column 10, lines 25-30).

Tsujihara et al. does not specifically teach the composition consisting of 1 w/v% to 20 w/v% of the camptothecin derivative, buffer, and water, which is adjusted to pH 5-8 with said buffer (instant claim 20). Tsujihara et al. does not specifically teach the composition wherein the ionic strength of the buffer is 0.2 or less than 0.2 (instant claim 25). Tsujihara et al. does not specifically teach the composition wherein the pH is adjusted to 5 to 7.5 (instant claim 26).

Harada 2001 teaches the embodiments of an i.v. bolus injection of T-0128 at a dose equivalent to 1, 2, 5, 10 or 25 mg of T-2513/kg as a 2 ml/kg solution (page 74, left column, paragraph 1). Harada 2001 discloses the dose equivalent to be based on the amount of T-2513 bound to CM dextran (abstract), or the amount of T-2513 in T-0128. Harada 2001 discloses the content of T-2513 in T-0128 is 4.5-5.5% w/w, or approximately 5% w/w. Therefore a dose equivalent to 1 mg of T-2513 is 20 mg of T-0128, and the disclosed i.v. bolus injections contain approximately 20, 40, 100 or 500 mg of T-0128 in 2 mL, or approximately 1, 2, 5, 10 or 25 w/v%.

Fassberg et al. teaches it is known that the lactone functionality of camptothecin plays an important role in the compound's biological activity and that the hydrolysis of the lactone is pH-dependent (page 676, right column, paragraph 2). Fassberg et al.

teaches camptothecin in a solution consisting of water and buffer at varying concentration (page 681, table VI at top of page) and that equilibrium position of lactone is largely to the hydrolyzed form at pH > 8 (page 681, right column, paragraph 1). Fassberg et al. teaches the embodiment of a solution consisting of camptothecin in water and phosphate buffer at pH 6.60 (page 681, table VI at top of page).

Bates et al. teaches that physiological plasma has an ionic strength of 0.16 mol/kg, (page 1295 abstract and first paragraph of article). Bates et al. teaches that the standard for physiological plasma is pH 7.4 (Page 1295, right column, paragraphs 3-4).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Tsujihara et al. in view of Harada 2001 and Fassberg et al. One of ordinary skill in the art would have been motivated to combine Tsujihara et al. in view of Harada 2001 and Fassberg et al. to select the concentration of approximately 1, 2, 5, 10 or 25 w/v% because Tsujihara et al. teaches the optimizing the dosage of said compound in the form of a liquid preparation such as for intravascular injection and Harada 2001 teaches the dosing of said compound T-0128 in the form of a liquid preparation for intravascular injection. One of ordinary skill in the art would have been motivated to combine Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. to give a composition consisting of camptothecin derivative, buffer, and water at an ionic strength of 0.16 and pH 6.60 because Fassberg et al. teaches a solution consisting of camptothecin in water and phosphate buffer at pH 6.60 and the desirability of lower pH to shift the equilibrium to the lactone form and one of ordinary skill in the art would desire to formulate a liquid preparation for intravascular injection to

be the same tonicity, or ionic strength, and pH as the physiological plasma that it will be injected into.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsujihara et al. (US Patent 5,837,673, issued 17 Nov 1998, cited in PTO-892) in view of Harada 2001 (Journal of Controlled Release, 2001, 71, p71-86, cited in PTO-892) and Fassberg et al. (Journal of Pharmaceutical Sciences, 1992, 81(7), p676-684, cited in PTO-892) and Bates et al. (Analytical Chemistry, 1978, 50(9), p1295-1300, cited in PTO-892) as applied to claims 20 and 25-28 above, and further in view of the '817 Patent (US Patent 5,340,817, issued 23 Aug 1994, of record).

Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. teaches as above.

Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. does not specifically teach a lyophilized drug composition of said liquid prepration (instant claim 29).

The '817 Patent teaches a camptothecin analog that is a water-soluble derivative of camptothecin bound to an amino acid or peptide (column 8, lines 19-22) "incorporated into a solution or suspension. The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution... buffers such as acetates, citrates or phosphates..." (column 13, lines 14-27). The '817 Patent teaches the lyophilization of liquid preparations to provide the camptothecin derivatives (column 18, lines 30-31 and 52-53).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. and further in view of the '817 Patent by using of a known technique to improve similar devices (methods, or products) in the same way. It would have been obvious to one of ordinary skill in the art to use the known technique of lyophilization to improve Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. in the same way with a reasonable expectation of success because the '817 Patent teaches lyophilization of liquid preparations to provide the camptothecin derivatives and said compounds incorporated into a solution. One of ordinary skill in the art would have been motivated to combine Tsujihara et al. in view of Harada 2001 and Fassberg et al. and Bates et al. and further in view of the '817 Patent because one of ordinary skill in the art would understand it is easier to store a dry product that one can incorporate into a solution by adding a sterile diluent such as water for injection than to store a liquid product.

Claims 22 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harada 2001 (Journal of Controlled Release, 2001, 71, p71-86, cited in PTO-892) in view of Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) and Bates et al. (Analytical Chemistry, 1978, 50(9), p1295-1300, cited in PTO-892).

Harada 2001 discloses the embodiments of an i.v. bolus injection of T-0128 at a dose equivalent to 1, 2, 5, 10 or 25 mg of T-2513/kg as a 2 ml/kg solution in 0.9% NaCl (page 74, left column, paragraph 1). Harada 2001 discloses the dose equivalent to be

based on the amount of T-2513 bound to CM dextran (abstract), or the amount of T-2513 in T-0128. Harada 2001 discloses the content of T-2513 in T-0128 is 4.5-5.5% w/w, or approximately 5% w/w. Therefore a dose equivalent to 1 mg of T-2513 is 20 mg of T-0128, and the disclosed i.v. bolus injections contain approximately 20, 40, 100 or 500 mg of T-0128 in 2 mL, or approximately 1, 2, 5, 10 or 25 w/v%.

Harada 2001 does not specifically teach the composition consisting of said buffer and which is adjusted to pH 5-8 with said buffer (instant claims 22). Harada 2001 does not specifically disclose or teach a composition having an ionic strength of 0.2 or less than 0.2 (instant claim 25).

Harada 2001 teaches the determination of T-0128 concentration in plasma and tissue by suspending cell homogenate in phosphate buffered saline at pH 7.0 (page 75, left column, paragraph 2).

Okuno et al. teaches chromatographic analysis of T-0128 in a 0.2M phosphate buffer at pH 6.9 in water (page 2989, left column, section Characterization of T-0128).

Bates et al. teaches that physiological plasma has an ionic strength of 0.16 mol/kg, (page 1295 abstract and first paragraph of article). Bates et al. teaches that the standard for physiological plasma is pH 7.4 (Page 1295, right column, paragraphs 3-4).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teaching of Harada 2001 in view of Okuno et al. and Bates et al. to give the i.v. bolus injection of T-0128 in phosphate buffered saline at pH 7.0. One of ordinary skill in the art would have been motivated to combine the teaching of Harada 2001 in view of Okuno et al. with a reasonable expectation of success because Harada

2001 teaches the composition for i.v. injection in saline and one of ordinary skill in the art would have understood that phosphate buffered saline is used to mimic the pH and tonicity of bodily fluids, and Okuno et al. teaches T-0128 analyzed in 0.2M phosphate buffer at pH 6.9 in water suggesting phosphate buffer is a chosen buffer system for compound T-0128. Therefore one of ordinary skill in the art would have been motivated to combine the teaching of Harada 2001 in view of Okuno et al. to make said composition for i.v. injection of T-0128 at approximately 1, 2, 5 or 10 w/v% that comes close to the pH and isotonicity of bodily fluids by using phosphate buffered saline adjusted to pH 7.0 having an ionic strength of 0.16.

Amended Claims 21-23 and 25-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harada 2001 (Journal of Controlled Release, 2001, 71, p71-86, cited in PTO-892) in view of Okuno et al. (Cancer Research, 2000, 60, p2988-2995, of record) and Bates et al. (Analytical Chemistry, 1978, 50(9), p1295-1300, cited in PTO-892) and further in view of Inoue et al. (WIPO Publication WO97/46260, published 11 Dec 1997, of record) and in view of the '817 Patent (US Patent 5,340,817, issued 23 Aug 1994, of record). As the WIPO Publication WO97/46260 is in Japanese, the national stage application issued as US Patent 6,436,912 is provided as an English-language equivalent and referenced as Inoue et al. herein.

Harada 2001 in view of Okuno et al. and Bates et al. teaches as above.

Harada 2001 in view of Okuno et al. and Bates et al. does not specifically teach the liquid composition consisting of one or more stabilizers selected from an alkali metal

carbonate and an alkali metal hydrogen carbonate (instant claims 21 and 23). Harada 2001 in view of Okuno et al. does not specifically teach a lyophilized drug composition which is prepared by lyophilizing said liquid preparation (instant claim 29).

Inoue et al. teaches drug complexes comprising a drug compound bound to a carboxylalkyl dextran by means of a spacer comprising peptide-bounded amino acids (abstract). Inoue et al. teaches said drug includes camptothecin or derivatives thereof (column 6, lines 20-30). Inoue et al. teaches said spacer comprising glycine-glycine-glycine (column 8, lines 30-35). Inoue et al. teaches said drug complexes in the form of a lyophilized product and pharmaceutical additives such as solubilizers, pH modifiers and stabilizers available in the field of the art can be used (column 13, lines 55-65).

The '817 Patent teaches a camptothecin analog that is a water-soluble derivative of camptothecin bound to an amino acid or peptide (column 8, lines 19-22) "incorporated into a solution or suspension. The solutions or suspensions may also include the following components: a sterile diluent such as water for injection, saline solution... buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose." (column 13, lines 14-27). The '817 Patent also teaches oral liquid compositions of a camptothecin analog, such as capsules, elixirs, suspensions, syrups, which generally include an inert diluent or an edible carrier and incorporated with excipients (column 13, lines 29-36). The '817 Patent teaches the lyophilization of liquid preparations to provide the camptothecin derivatives (column 18, lines 30-31 and 52-53). The '817 Patent teaches the

camptothecin compound is compatible in solution with the excipient sodium bicarbonate, an alkali metal hydrogen carbonate (column 18, lines 15-20 and 40).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine Harada 2001 in view of Okuno et al. and Bates et al. and further in view of Inoue et al. and in view of the '817 Patent. Harada 2001, Okuno et al. and Inoue et al. are drawn to drug complexes comprising a drug compound bound to a carboxylalkyl dextran by means of a spacer comprising peptide-bounded amino acids, said drug encompassing camptothecin derivatives. Okuno et al., Harada et al. and the '817 Patent are drawn to camptothecin derivatives. One of ordinary skill in the art would have a reasonble expectation of success in combining Okuno et al. in view of Harada et al. and further in view of Inoue et al. and in view of the '817 Patent because Inoue et al. teaches pharmaceutical additives available in the field of the art can be used with the drug complexes taught by Inoue et al. and the '817 Patent teaches pharmaceutical additives compatible with camptothecin derivatives.

Conclusion

No claim is found to be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jonathan S. Lau whose telephone number is 571-270-3531. The examiner can normally be reached on Monday - Thursday, 9 am - 4 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jonathan Lau
Patent Examiner
Art Unit 1623

/Shaojia Anna Jiang/
Supervisory Patent Examiner
Art Unit 1623